Carcinoma of the uterine cervix is the second most common cancer among women worldwide. Just over half (52%) of those diagnosed with the cervical cancer will eventually die from the disease. In the United Kingdom cervical cancer has remained the 16th most commonly diagnosed malignancy, with an annual incidence of around 3 000 cases, and around 1 000 women die from the disease every year. However, the mortality rates from cervical cancer in 2007 were nearly 70% lower than they had been 30 years earlier. It is the National Health Service (NHS) Cervical Screening Programme that takes the credit for this remarkable achievement. In South Africa cervical cancer is second only to carcinoma of the breast and is estimated to claim the lives of around 3 000 of the approximately 5 700 women who are diagnosed with the disease each year. The age-standardised mortality rate (per 100 000 women) is 14.5 (this figure was 2.4 in the United Kingdom in 2007). The population at risk (those women 15 years and older) amounts to 16.84 million in South Africa. Around 21% of South African women are thought to carry human papilloma virus (HPV), which is widely accepted as the causative agent behind invasive cervical carcinoma and its precursors. The high-risk HPV types 16 and 18 are responsible for 63% of invasive cervical cancers. The HPV vaccination programme was launched in the UK in September 2008. There is no organised HPV vaccination programme currently in South Africa although the vaccine is available on prescription. While HPV vaccination may well change the epidemiology of the disease in the future, cervical screening remains the main weapon in the war against cervical cancer for the foreseeable future.

The Pap smear

The cervical smear test, first described by the Greek gynaecologist Georgius Papanicolaou, consists of cytological examination of cells scraped off the neck of the womb. Precancerous cells are estimated to take 10 - 15 years to develop into invasive cancer. The majority are squamous cell carcinoma. The Papanicolaou (or Pap) smear can identify changes ranging from mere HPV infection to high-grade abnormalities (as well as infections other than HPV, e.g. herpes simplex virus and Candida yeast), making early intervention and cure possible. It is considered the most successful cancer screening method ever discovered.

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Liquid-based cytology

Table I. Comparison of the Bethesda and the British Society for Clinical Cytology (BSCC) classification systems for cervical cytology

<table>
<thead>
<tr>
<th>Bethesda classification</th>
<th>BSCC classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for intraepithelial lesion or malignancy</td>
<td>Negative</td>
</tr>
<tr>
<td>Unsatisfactory for evaluation</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Atypical squamous cells of undetermined significance (ASC-US)</td>
<td>Borderline nuclear change</td>
</tr>
<tr>
<td>Atypical squamous cells cannot exclude H-SIL (ASC-H)</td>
<td></td>
</tr>
<tr>
<td>Atypical endocervical, endometrial or glandular cells (not otherwise specified or specify)</td>
<td></td>
</tr>
<tr>
<td>Atypical endocervical or glandular cells favour neoplasia</td>
<td></td>
</tr>
<tr>
<td>Low-grade squamous intraepithelial lesion (L-SIL)</td>
<td>Mild dyskaryosis</td>
</tr>
<tr>
<td>High-grade squamous intraepithelial lesion (H-SIL)</td>
<td>Moderate dyskaryosis</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Severe dyskaryosis</td>
</tr>
<tr>
<td>Endocervical carcinoma in situ</td>
<td>?Invasive</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>?Glandular neoplasia</td>
</tr>
<tr>
<td>Endocervical</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td></td>
</tr>
<tr>
<td>Extraterter</td>
<td></td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td></td>
</tr>
</tbody>
</table>

UK the British Society for Clinical Cytology (BSCC) classification is more commonly used (Table I).

The Pap smear is usually carried out by a general practitioner or nurse at a primary care or community clinic. Cervical cells are harvested using a disposable spatula, then spread on a glass slide and fixed. The slide is forwarded to a hospital laboratory, where it is stained and examined by a cytologist. Patient management depends on the cytology result. Approximately 8% of Pap smear tests cannot be interpreted because of problems with sample collection or preparation (such as insufficient cervical cells), or the presence of inflammatory cells, blood or mucus, which obscure the sample. Women with inadequate test results are required to attend for a repeat test, which is inconvenient and may cause anxiety.

What is liquid-based cytology?

Liquid-based cytology (LBC) is a new method of cervical cell sample preparation. Samples are collected in the usual way, but a brush-like device (cytobrush) is used rather than a spatula (Fig. 1). The head of the device is rinsed or broken off into a vial of preservative fluid so that most or all of the cervical cells are retained. Samples are transported to the laboratory, where they are mixed to disperse the cells. Cellular debris, such as blood or mucus, is removed and a thin layer of cervical cells is deposited on a microscope slide, which is then stained. The cytological diagnostic criteria and the diagnostic categories are the same as for the conventional Pap smear (Table I).

Liquid-based cytology (LBC) is a new method of cervical cell sample preparation. Samples are collected in the usual way, but using a brush-like device (cytobrush) rather than a spatula.

LBC has been in use since 1996 in the USA and has almost completely replaced conventional cytology there, but not in all European countries. In England and Scotland exhaustive meta-analysis of pilot studies showed that LBC could curb the high rate of unsatisfactory smears, and the conversion to LBC was completed in the UK in October 2008. In continental Europe, funding agencies were unwilling to provide extra funding for LBC. Therefore, in the Netherlands, Switzerland and France the pathologist has to decide which method to use, with the same fee for both methods.

Comparison of liquid-based cytology and Pap smear

The main criteria used to assess the effectiveness of the LBC method compared with the Pap smear are the rate of ‘inadequate’ specimens and the sensitivity and specificity of each method. A pilot study preceding the adoption of LBC by the NHS in the UK that took place at three sites in England over a 12-month period showed a statistically significant decrease in the number of inadequate samples, from 9.1% with Pap slides to an average of 1.6% with LBC (87% reduction, p<0.0001). In keeping with the pilot study results, the rate of inadequate tests taken in the NHS Cervical Screening Programme fell from over 9% before the introduction of LBC to 2.5% in 2008 - 2009. The majority of 34 studies reporting the rate of inadequate samples noted that the rate was reduced with LBC.
of LBC decreased cytological glandular neoplasia referrals, this did not happen at the expense of missing pre-invasive and invasive cancers.\textsuperscript{10} The few studies that investigated inter-observer variability using LBC in cervical cytology found that it was superior to the conventional method, particularly for squamous intraepithelial lesions.\textsuperscript{11}

**The main criteria used to assess the effectiveness of the LBC method compared with the Pap smear are the rate of ‘inadequate’ specimens and the sensitivity and specificity of each method.**

A further advantage of the LBC method is an improved means of slide preparation, which is carried out in the pathology laboratory by experienced technical staff, producing a more even quality of slides. The samples are technically superior to Pap smears. The samples are spun and the cells become dispersed, resulting in a more even distribution on the slide, instead of the multilayered clumps of cells on conventional smears. The cells are concentrated in a dot in the middle of the slide, making them easier and much faster to read than the Pap smear (Fig. 2). Unwanted material, such as blood or mucus, may be removed during the preparation process (Figs 3 - 7). Any surplus cells may be stored in the preservative vial in the laboratory, and additional slides may be prepared in case of diagnostic uncertainty or for teaching.

In the English pilot study there was a 5-minute reduction in the time required for smear taking and consultation with LBC (around 8 minutes compared with 13 minutes for the Pap smear). The productivity of laboratories increased with LBC because 9% more slides could be primary screened per hour; the number of formal breaks remained unchanged.\textsuperscript{9} LBC is apparently an easier method for sample takers.\textsuperscript{12} The implementation of LBC was said to have been received favourably both by smear takers in primary care and by laboratory staff.\textsuperscript{9}

Various diagnostic systems have been developed for LBC. In the UK as well as in Europe, the USA and South Africa, two main products have been trialled, Surepath\textsuperscript{®} (BD Diagnostics) and Thinprep\textsuperscript{®} (Hologic\textsuperscript{®}). These are also both Food and Drug Administration approved.\textsuperscript{13} The English report found that the rate of inadequate smears in the pilot was lower at the sites using SurePath\textsuperscript{®} than at those using ThinPrep\textsuperscript{®}. In baseline estimate the cost per smear was found to be slightly higher with ThinPrep\textsuperscript{®} than with conventional cytology (by £1.31 - £1.47 depending on the preparation machine used) and slightly lower with SurePath\textsuperscript{®} than conventional cytology (by £0.92).\textsuperscript{9} Overall it was thought that increased capital costs of £50 000 and consumables costs of £2.50 per test may be
Liquid-based cytology

offset by savings from the reduction in the number of inadequate samples and a quicker diagnosis, to give a gross saving of £0.89 per LBC test compared with the Pap smear.

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Notwithstanding the higher costs, LBC has now been successfully trialled in South African pathology laboratories. It is already in routine use in some private laboratories and is expected to be rolled out in the National Health Laboratory Service within the next few years. Some private laboratories have reduced the price to match conventional Pap smear costs in order to encourage more widespread use of LBC.

What does it mean for general practitioners?

Of the 13.4 million women aged 25 - 64 years eligible for cervical screening in England, 78.9% had been screened within the previous 5 years. Just under 3.7 million samples were examined by pathology laboratories in 2009 - 2010. The South African National Screening Programme for Cervical Cancer proposes three free smears in a lifetime, with a 10-year interval for Cervical Cancer proposes three free laboratories in 2009 - 2010. The South African National Screening Programme in South Africa within the next few years. Some private laboratories have started using LBC in South Africa, even lowering the price to match that of Pap smear.

There are two main diagnostic systems available: SurePath® and ThinPrep®. Some private laboratories have started using LBC in South Africa, even lowering the price to match that of Pap smear.

SurePath®
- The head of the brush is simply removed from the stem and then placed into the vial of fixative.
- When the lid has been screwed on, the vial should be shaken to ensure that the cells do not cling to the device.

ThinPrep®
- The brush is rinsed into the fixative vial using a vigorous swirling motion.
- The brush is firmly pushed into the bottom of the vial at least 10 times, forcing the bristles apart.
- The brush should be inspected for the presence of any residual material, which is removed by passing the brush over the edge of the fixative vial.
- It should be ensured that the material reaches the liquid or it will not be preserved.
- The cap is then tightened so that the torque line passes the torque line on the vial.
- If any material has been placed on the edge of the vial, it should be given a shake.

The speculum may be removed once the sample has been placed in the fixative.

IN A NUTSHELL

- LBC is superior to conventional Pap smears in every respect with the exception of cost.
- There are two main diagnostic systems available: SurePath® and ThinPrep®.
- Some private laboratories have started using LBC in South Africa, even lowering the price to match that of Pap smear.
- LBC is expected to be widely rolled out as part of the National Cervical Screening Programme in South Africa within the next few years.
- This new technique promises to save workload and time for the primary care practitioner.
- General practitioners taking cervical cytological samples should familiarise themselves with the technical aspects of taking samples for LBC.

References available at www.cmej.org.za